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Host–guest interactions and their role in enantioselective hydrogenation of α -keto esters

An analysis of model systems

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Abstract

The interaction between cinchonidine and methyl pyruvate has been proposed as the key step leading to enantiodifferentiation in the enantioselective hydrogenation of α -ketoesters. In the present work, we employ *ab initio* MP2/6-31G(d) and MP2/6-31G(d,p) methods to carry out an analysis of the most relevant kind of interactions operating in representative model systems. These interactions are discussed in terms of orbital superposition and dipolar interaction. When approaching H₂CO to NH₃ at distances lower than 3.4 Å, orbital superposition is the predominant interaction, while at distances above 3.4 Å, both orbital superposition and dipolar interactions may contribute to stabilization, with a small prevalence of dipolar interactions. The stabilization energy at large distances (above 4.5 Å) is very small (about 0.5 kcal mol⁻¹), probably not enough to be responsible for the enantiodifferentiation process. Semiempirical calculations on the parent systems were also unable to reveal any special interaction which could be attributed to the enantiodifferentiation process. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

The increasing interest on asymmetric hydrogenation in heterogeneous catalysis has been stimulated by

the highly stereospecific catalytic systems that have been developed in the last two decades [1]. A large variety of carbonyl substrates has been tested, including α - and β -ketoesters [2], activated ketones [3] and others α,β -unsaturated carbonyl compounds [4]. The main chemical characteristic in all substrates tested so far, where high degree of enantioselectivity was achieved, is the α,β -unsaturation to a carbonyl (or

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carboxyl) moiety which undergoes hydrogenation. In order to accomplish the desired enantioselectivity, the reaction must be carried out in the presence of a chiral modifier [5].

Enantioselective hydrogenation of α -ketoesters over Pt/Al₂O₃ catalyst in the presence of alkaloid modifiers has been reported with enantiomeric excess of over 90% with high conversions [2]. The most effective chiral modifiers that have been reported are cinchona alkaloids dihydroderivatives, such as dihydrocinchonidine and dihydrocinchonine. Two rigid rings, a quinoline and a quinuclidine ring, which are bonded together by a chiral carbon center that seems to be essential for the enantioselective reaction, characterize these molecules.

Although much has been published about this reaction, its mechanism is not yet fully understood [1]. In special, there is a continuous discussion on the role of the chiral modifier in the induction of enantioselectivity and, therefore, on its interaction with the pro-chiral substrate [1] and with the metal surface [6]. At least two lines of arguments can be clearly identified in the literature [7,8].

In one of them, a crucial role is attributed to the metallic surface in the process of enantioselection [7]. It is assumed that the modifier–substrate interaction takes place on the metallic surface, creating a “modified chiral site” which is hydrogenated, thereby leading to asymmetric induction [7]. Indeed, recent studies showed that dihydrocinchonidine adsorbs on a Pt(111) surface with the quinoline moiety almost parallel to the Pt surface [6]. Similarly, ethyl pyruvate also adsorbs on the Pt(111) surface in a tilted orientation, with the negatively charged end of ethyl pyruvate pointing toward the metal surface [9,10].

In an opposite line, it has been supposed that the interaction between modifier and substrate takes place in the bulk liquid-phase without participation of the metallic surface [8]. In this approach, the modifier would interact with the substrate, forming a host–guest complex, which is then hydrogenated on the catalyst surface. The enantioselective process would occur, therefore, upon formation of the modifier–substrate complex, which leads to asymmetric induction. This view was mainly based on the observation that the circular dichroism spectra of cinchonidine is altered by addition of ethyl pyruvate [8], what was interpreted

as a strong indication that cinchonidine interacts with ethyl pyruvate in the liquid-phase.

In the present paper, based on ab initio and semiempirical molecular orbital calculations, we give some evidences that the energy and the geometry of the modifier–substrate complex (host–guest complex formation), per se, are not enough to explain the observed enantioselectivity. In some way, the catalytic surface participates in the step leading to enantiodifferentiation.

2. Calculations

Ab initio methods, at the MP2/6-31G(d) and MP2/6-31G(d,p) levels [11], were used to study the interaction between representative model systems and to calculate structures and energies. Geometries were fully optimized following some restrictions as discussed below. For stationary points, the second derivative matrix was calculated in order to identify the nature of that stationary point. The energy of interaction between species forming a loose van der Waals complex was corrected for basis set superposition error (BSSE) using the method of counterpoise correction [12], where the energy of each subunit was calculated with ghost atoms replacing the atoms of the second subunit. The GAUSSIAN98 package [13], running on a Pentium II and on workstations, was used in the ab initio calculations. The semiempirical AM1 method [14] was employed to study the interaction between cinchonidine, in its closed and open conformations [15], and methyl pyruvate. In these cases, geometries were fully optimized without any constraint. The MOPAC93 package [16], running on a Pentium II, was used in the semiempirical calculations.

3. Results and discussion

The main goal of our work is to identify, at a molecular level, the chemical basis for the modifier–substrate interactions. We started following the argumentation of Margitfalvi et al. [8]. These authors suggested that the main interaction between methyl pyruvate (MP) and cinchonidine involves the nitrogen lone electron pair of the quinuclidine ring

of cinchonidine, which would act as a nucleophile towards the electron deficient carbon atom of the keto carbonyl group of MP. Additionally, a certain type of π - π interaction between the quinoline π system and the conjugated double bond system of MP afforded the second point of anchorage. The last interaction would be equivalent to the traditional π -stacking interaction well-known in organic chemistry [17]. The synergetic effect of both interactions would increase carbonyl reactivity (rate acceleration effect) and direct the pyruvate molecule to a specific orientation (shielding effect), which would result in a chiral non-racemic lactate after hydrogenation.

3.1. Interaction between formaldehyde and ammonia

Our analysis started by calculating the interactions between the model systems H_2CO (formaldehyde) and NH_3 (ammonia). These systems have already been investigated before [18,19], although not in the context dealt with in the present work, where we specifically address the nature of the forces stabilizing the final $\text{H}_2\text{CO}/\text{NH}_3$ complex. This is the simplest system that can be designed to represent the kind of interactions supposed to take place in the cinchonidine–MP system. The same kind of interactions present in the main system should also be observed in this model system, in special dipolar interactions and molecular orbital su-

perposition. The small size of the model system makes possible the use of high quality ab initio calculations.

Disregarding weak dispersion forces, there are two main types of interactions that can be important to the stabilization of a $\text{H}_2\text{CO}-\text{NH}_3$ complex: dipolar interactions and orbital superposition (Fig. 1). Orbital superposition would be maximal when the lone electron pair of the ammonia molecule approaches the formaldehyde molecule in a direction perpendicular to the CO bond, above or below the carbon atom (Fig. 1a), resulting in a $\text{O}=\text{C}\cdots\text{N}$ angle of 90° . In this orientation, there is a maximum in the superposition between the lone electron pair of the nitrogen atom — the HOMO of ammonia — and the antibonding π^* orbital of the CO double bond — the LUMO of formaldehyde — which has its highest density on the carbon atom. This orientation also corresponds to vanishing dipolar interaction, since both dipoles are disposed perpendicular to each other. On the other hand, the arrangement given in Fig. 1b affords the orientation of maximum stabilization between the two dipoles. The collinear alignment between the dipoles of formaldehyde and ammonia results in an arrangement where the $\text{O}=\text{C}\cdots\text{N}$ angle is 180° . In this case, the orbital superposition vanishes, since the lone electron pair of the nitrogen atom superposes equally with the positive and the negative lobes of the antibonding π^* orbital of the carbon–oxygen double bond.

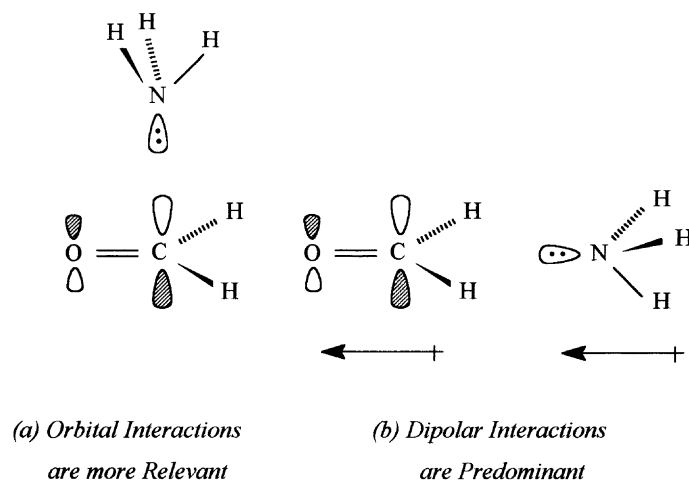


Fig. 1. (a) Orbital and (b) dipolar interactions of the $\text{H}_2\text{CO}-\text{NH}_3$ complex. The orbital depicted on formaldehyde is the LUMO, the π^* -C=O antibonding orbital, which has higher density on the carbon atom.

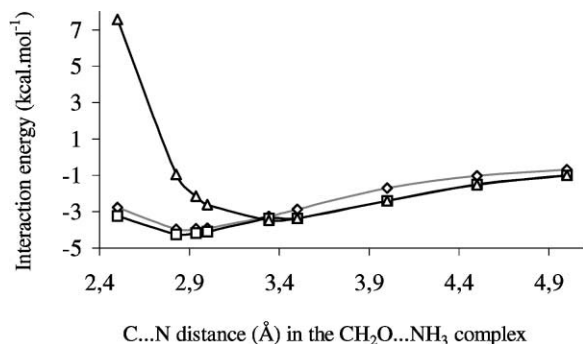


Fig. 2. MP2/6-31G(d) potential energy profile for approximation between formaldehyde and ammonia along the minimum energy pathway (\square); a pathway with the $\text{O}=\text{C}\cdots\text{N}$ angle equal to 180° (\triangle); a pathway with the $\text{O}=\text{C}\cdots\text{N}$ angle equal to 90° (\diamond).

Based on the above reasoning, we calculated, at the MP2/6-31G(d) level, the potential energy profile for approaching ammonia towards formaldehyde, along the two directions indicated in Fig. 1, as a function of the $\text{C}\cdots\text{N}$ distance for several points between 2.5 and 5.0 Å. A corresponding potential energy profile following the pathway of minimum energy was also calculated (Fig. 2).

At large distances, above 3.4 Å, the three pathways have similar energy. The pathway where dipolar interaction is favored ($\text{O}=\text{C}\cdots\text{N} = 180^\circ$) has somewhat lower energy than that where orbital superposition is favored ($\text{O}=\text{C}\cdots\text{N} = 90^\circ$), but the energy difference between both pathways is very small. This means that the potential energy surface for approaching the NH_3 molecule to the H_2CO molecule at distances above 3.4 Å is very flat. All orientations within the semi-sphere defined by the angle $\text{O}=\text{C}\cdots\text{N} \geq 90^\circ$ may serve as an adequate arrangement for interaction between the two molecules, contrary to the reaction window model proposed by Margitfalvi et al. [8]. Although, the arrangement where the $\text{O}=\text{C}\cdots\text{N}$ angle is equal to 180° has lower energy than that where the $\text{O}=\text{C}\cdots\text{N}$ angle is 90° , the small difference to approach in other directions do not justify the definition of a reaction window. A plot of the $\text{O}=\text{C}\cdots\text{N}$ angle as a function of the $\text{C}\cdots\text{N}$ distance when NH_3 approaches H_2CO through the pathway of lower energy (Fig. 3) shows that for distances above 3.5 Å, the dipolar interaction predominates, resulting in a $\text{O}=\text{C}\cdots\text{N}$ angle of 180° . However, as the NH_3 and

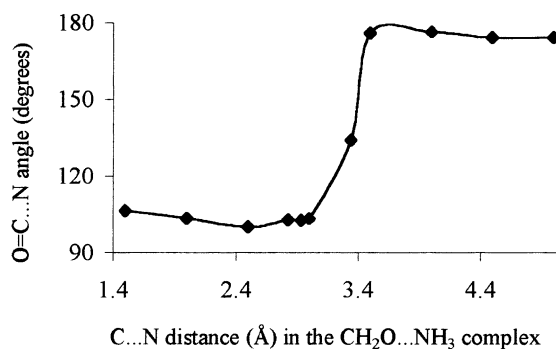


Fig. 3. $\text{O}=\text{C}\cdots\text{N}$ angle ($^\circ$) along the minimum energy pathway for approximation between formaldehyde and ammonia.

H_2CO molecules come closer together, orbital interaction becomes more relevant and the NH_3 molecule moves to an orientation where the $\text{O}=\text{C}\cdots\text{N}$ angle is about 105° . In the position of minimum energy, the $\text{O}=\text{C}\cdots\text{N}$ angle has a value of 105° with a $\text{C}\cdots\text{N}$ distance of 2.9 Å. Further approximation of the two molecules results in strong predomination of orbital interaction and the geometry around the carbon atom approaches the tetrahedral arrangement. The geometry parameters given above are similar to those obtained before [18].

The stabilization energy (given as the difference between the energy of the complex and the energy of the isolated species, formaldehyde and ammonia) in the arrangement of minimum energy is $4.2 \text{ kcal mol}^{-1}$. After correction for BSSE, this value is reduced to $2.4 \text{ kcal mol}^{-1}$. As the distance between the two subunits increases, the stabilization energy is steadily reduced. At a distance of 4.5 Å, the mean distance calculated for the complex between cinchonidine and MP, the interaction energy is only $2.4 \text{ kcal mol}^{-1}$. After correction for BSSE this should be reduced to a value close to zero. Calculations of the energy for interaction between two collinear dipoles [20] with values of $1.967D$ (NH_3) and $2.840D$ (H_2CO) separated by a distance of 2.9 Å (the minimum energy distance for interaction between NH_3 and H_2CO) lead to a stabilization of $3.3 \text{ kcal mol}^{-1}$. As the energy between dipoles decreases as R^{-3} , this interaction energy is reduced to $0.9 \text{ kcal mol}^{-1}$ when the distance between the two dipoles increases to 4.5 Å. Therefore, the small stabilization energy calculated for the

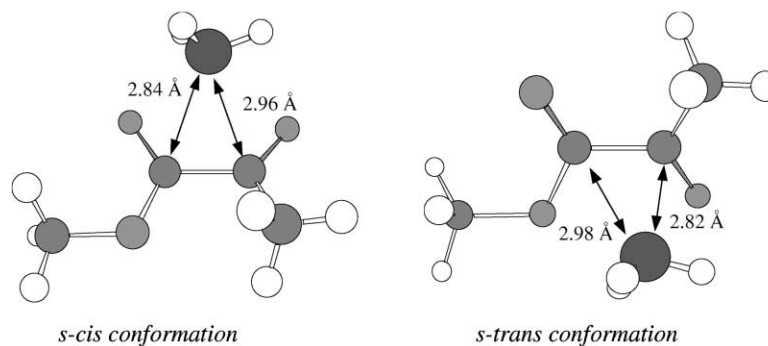


Fig. 4. Complexes between methyl pyruvate and ammonia.

$\text{NH}_3 \cdots \text{H}_2\text{CO}$ complex at distances above 3.0 \AA is essentially due to dipolar interaction. Note that the above calculations are for instantaneous interactions at the orientation of minimum energy. The average interaction energy when considering a large number of randomly oriented molecules will fall off with R more rapidly, since the tendency of dipoles to align decreases with distance. Therefore, in the bulk, the interactions will be even weaker.

3.2. Interaction between MP and ammonia

The point we should address now is how these results can be transferred to the much larger system cinchonidine–MP. We have also calculated the interaction between NH_3 and MP at the MP2/6-31G(d,p) level. At this level, the ammonia molecule interacts with MP in an orientation almost normal to the plane of MP, approximately equidistant from both carbonyl carbons (Fig. 4). This orientation is essentially equivalent to that found at the Hartree–Fock level [21]. The $\text{C} \cdots \text{N}$ distances in the cinchonidine–MP complex are very similar to those found in the smaller model system $\text{NH}_3\text{--H}_2\text{CO}$. However, the interaction energy is considerably higher in this case ($7.3, 3.9 \text{ kcal mol}^{-1}$ after BSSE) than in the case of the smaller system. As the orientation of the NH_3 molecule indicates, this is essentially due to orbital interactions. As there are two carbonyl carbons to interact, the interaction energy is consequently increased. Due to the computational cost, it was not possible to try approaching the NH_3 molecule in different pathways as was done for the smaller system. However, when starting the opti-

mization at large distances, with the nitrogen atom of the NH_3 molecule in the same plane as that of MP, it converges directly to the arrangements shown in Fig. 4. Therefore, orbital interactions are predominant in this case and the NH_3 molecule approaches the MP in an orientation normal to the plane holding the carbonyl bonds. These results lead us to the conclusion that, although in the smaller system dipolar and orbital interactions can almost equally contribute to the complex stabilization, in the case of the interaction between NH_3 and MP orbital interactions clearly predominates. This is most probably due to steric repulsion between the methyl group of MP and the ammonia molecule. These results indicate that the interaction between cinchonidine and MP should also occur in an orientation favoring orbital superposition with the nitrogen atom of the quinuclidine moiety in a position normal to the plane of MP.

3.3. Benzene–formaldehyde interaction

In addition to the $\text{O}=\text{C} \cdots \text{NR}_3$ interaction discussed above it has been argued that the second point of anchorage between cinchonidine and MP results from some kind of $\pi\text{--}\pi$ interaction between the π system of the quinoline ring and the π system of MP [8]. This kind of interaction has been interpreted in terms of $\pi\text{--}\pi$ -stacking effect [22], where both π systems are polarized due to the presence of the second π unity, and in terms of charge transfer complex [8], where HOMO–LUMO interactions take place with charge transfer from the aromatic ring system to the conjugated double bond system of MP. $\pi\text{--}\pi$ -Stacking inter-

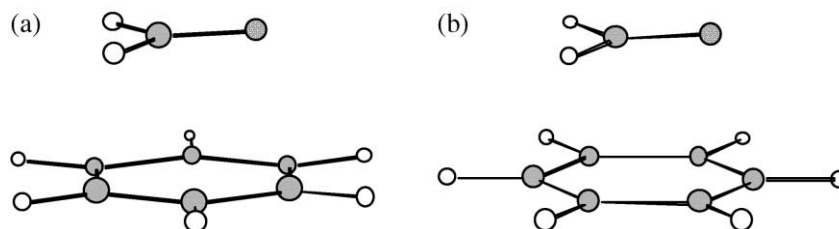


Fig. 5. Two possible arrangements for interaction between benzene and formaldehyde: (a) is the minimum energy arrangement, but (b) lies less than $0.1 \text{ kcal mol}^{-1}$ above.

actions are weak and have been observed mainly in solid state [23], although they have been supposed to originate stereoselective reaction in homogeneous liquid-phase catalytic processes [24]. Charge transfer complexes, in contrast, are usually more stable and have been observed in a set of reactions, for example leading to aromatic substitution [25].

In order to simulate these interactions, we calculated (at the MP2/6-31G(d) level) a set of complexes formed between benzene and formaldehyde. Two possible arrangements for complexes formed between these two molecules are shown in Fig. 5. Complex (a) is the minimum energy arrangement with a stabilization energy of $2.9 \text{ kcal mol}^{-1}$. This value is reduced to $0.7 \text{ kcal mol}^{-1}$ after correction for BSSE. In this complex, the distance between the H_2CO unity and the benzene molecule is about 3.3 \AA . The $\text{C}=\text{O}$ double bond of H_2CO aligns essentially parallel to the aromatic plane of benzene. In the second orientation of the H_2CO molecule, complex (b), the stabilization energy is essentially the same (less than $0.1 \text{ kcal mol}^{-1}$ above) as that found for complex (a). The distance from the H_2CO unity to the aromatic ring also does not change. These results indicate that the interaction between benzene and formaldehyde is very weak, probably due to self polarization of the π systems, since the orientation of the H_2CO unity in relation to the benzene ring makes no difference in terms of energy. If there was any kind of orbital interaction there should be also a preferential orientation of the H_2CO molecule.

3.4. Interaction between MP and cinchonidine

Due to the size of the system, it was not possible to calculate the interaction between cinchonidine and

MP at the correlated ab initio level. We have done, however, a detailed analysis of this interaction at the semiempirical AM1 level. The most stable conformations of cinchonidine are the open form A2 and the closed form C2, as described by Margitfalvi et al. [22] (Fig. 6). NMR experiments and ab initio calculations also showed that the open form is the most stable conformer of cinchonidine in apolar solvents. When going to polar solvents, however, the closed conformers are stabilized preferentially, becoming almost as stable as the open form [15]. Therefore, we calculated the interaction of MP with both the open and the closed conformers of cinchonidine.

Interaction of these conformers with MP results in the complexes shown in Fig. 7. We exhaustively searched for alternative structures for complexes between these two molecules. Several starting geometries were tried in each case. The representations shown in Fig. 7 are those for the most stable arrangement. Stabilization energies for complexes A2 and C2 in Fig. 7 are about 3.0 and $2.6 \text{ kcal mol}^{-1}$, respectively. These stabilization energies are essentially due

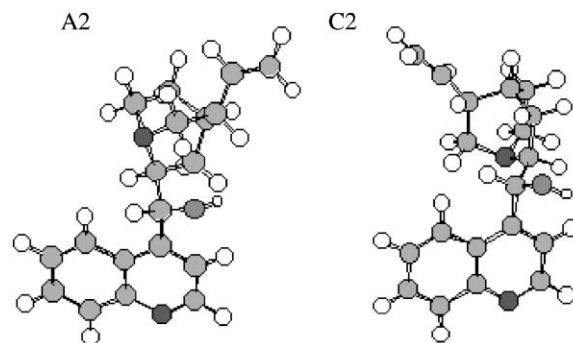


Fig. 6. Open (A2) and closed (C2) conformations of cinchonidine.

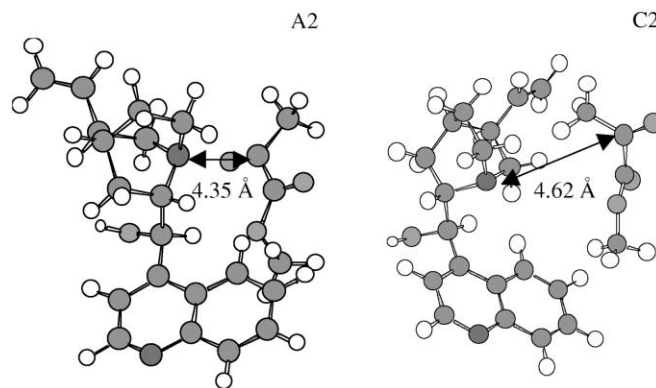


Fig. 7. Complexes between cinchonidine and methyl pyruvate.

to van der Waals dispersion forces, what has been confirmed by the calculation of the interaction between the much less polar 2-ethyl, 3-methyl-butadiene molecule and cinchonidine, which resulted in an interaction energy of $2.0 \text{ kcal mol}^{-1}$. The orientation of MP in relation to cinchonidine results in a $\text{C}\cdots\text{N}$ distance of 4.35 \AA in complex A2 and of 4.62 \AA in complex C2. The $\text{O}=\text{C}\cdots\text{N}$ angle is 172.9 and 156.4° in A2 and C2, respectively. Previous HF/6-31G(d,p) calculation on the interaction between protonated cinchonidine in its open conformation and MP [26] showed that for MP in a *s-trans* conformation, the complex yielding (*R*)-methyl lactate upon hydrogenation is more stable than the corresponding pro-(*S*) complex by $1.8 \text{ kcal mol}^{-1}$, whereas changing MP to a *s-cis* conformation, this energy difference is decreased to $0.2 \text{ kcal mol}^{-1}$. These results were obtained for complexes with the quinoline ring of cinchonidine and the MP molecule restricted to a coplanar orientation. In our case, we fully optimized the geometries of the complexes, therefore the MP molecule moves to a position farther away from the quinoline ring (Fig. 7). The relative orientation of the MP molecule in complexes A2 and C2 does not enable us to clearly distinguish between pro-(*R*) and pro-(*S*) complexes. Although, in these complexes one of the sides of MP seems to be shielded by the cinchonidine molecule, the energy difference for complexes where the MP is in an opposite orientation is very small, not enough to justify the observed enantiomeric excess.

Additionally, we tried to localize a structure where the π system of the quinclidine ring interacts with the

π system of MP. Although, several starting geometries were tested, no structure which show any indication of this interaction could be located. Even starting with a geometry where both π systems are in parallel planes, the optimization converges to structures where the π system of pyruvate is farther away from the π system of cinchonidine. Most probably this interaction is avoided by the repulsive steric forces acting between the methyl groups of MP and the quinoline moiety.

In view of the results presented above, it is hard to attribute the observed rate acceleration effect and enantiomeric excess only to the bulk interaction between cinchonidine and MP. Rate acceleration can be achieved either by direct activation via orbital superposition, as shown for example in the case of the ammonia/MP complex (Fig. 4), or by an indirect way, for example by restricting the orientation of MP upon complexation to positions where it could be hydrogenated more easily. Furthermore, in order to yield a non-racemic mixture after hydrogenation of MP, at least a second point of contact is required.

Our calculations show that orbital interaction may play some role, in special in the smaller systems, where the weak repulsive interactions allow the molecules to approach each other to distances where HOMO–LUMO interactions can take place. This is the case, for example, for the complexes between formaldehyde and ammonia and between MP and ammonia. However, when one part of the complex increases, the repulsive steric interactions become stronger and the moieties can not approach each other sufficiently to allow HOMO–LUMO interaction. This

is evidenced, for example, by the C···N distance in the cinchonidine/MP complexes which is considerably higher ($>4.3 \text{ \AA}$) than those calculated for either the $\text{CH}_2\text{O}/\text{NH}_3$ or the MP/NH_3 ($2.8\text{--}2.9 \text{ \AA}$) complexes. Dipolar interactions, which rivals orbital interactions in the smaller system ($\text{CH}_2\text{O}/\text{NH}_3$), seem to have no relevance in the case of the cinchonidine/MP complex. In the last case, the main attraction seems to originate in the attractive, non-covalent dispersion forces. A clear indication to this conclusion comes from the fact that the interaction between the less polar and less electrophilic species, 2-ethyl,3-methyl-butadiene and cinchonidine have almost the same energy as those between cinchonidine and MP. Of course, there may be some inaccuracy in the calculated relative energies due to limitations in the semiempirical AM1 method. Nevertheless, the AM1 method works very well for the model systems, with results in the same order as those obtained with the MP2 method.

With respect to the second point of contact, this does not seem to originate in the $\pi\text{--}\pi$ interaction as proposed before [8]. As shown for the case of the model system benzene/formaldehyde, the $\pi\text{--}\pi$ interaction is rather weak and should be even weaker in the case of the parent system cinchonidine/MP, where repulsive steric interactions are more relevant. Our AM1 results confirm this hypothesis. In none of the several complexes we calculated, this interaction showed up as of any relevance. We are led therefore to conclude that the metal surface must play a relevant role in the enantiodifferentiation process. A possible way for the interaction between cinchonidine and MP on the metal surface was recently given by Bürgi and Baiker [26].

4. Conclusions

Our calculations of model systems which simulate the most relevant interactions found in the cinchonidine–MP complex clearly show the following points. The contributions of dipolar interactions and orbital superposition to the stabilization of a NR_3/OCR_2 complex are essentially of the same magnitude, although at distances above 3.4 \AA between the NH_3 and CH_2O molecules, the dipolar interaction predominates slightly. This expands the ‘reaction window’ proposed by Margitfalvi and Tfirst [8] to a semi-sphere where the $\text{O}=\text{C}\cdots\text{NR}_3$ angle

can range from 90 to 180° . However, only the orbital superposition interaction, which is favored when the $\text{O}=\text{C}\cdots\text{NR}_3$ angle is about 90° , can activate the carbonyl group, leading to the experimentally observed acceleration in reaction rate. Therefore, this is the interaction which should prevail in the cinchonidine–MP complex. MP2 optimizations of a $\text{NH}_3\text{--MP}$ complex show that this is indeed the case since the most stable geometry has the NH_3 molecule in a line essentially normal to the molecular plane of MP. The second point of anchorage is still to be determined. The low energy calculated for the interaction between the model system, formaldehyde and benzene, most probably precludes this as being of any relevance to the enantiodifferentiation found in the cinchonidine–MP case. Therefore, we conclude that the energies and geometries of a host–guest cinchonidine–MP complex are, per se, not enough to explain the observed enantioselectivity. In some way, the catalytic surface must play an important role in these reactions, at least, in the step which determines the enantioselectivity. These studies are presently being carried out by our group.

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